Vivern – A Virtual Environment for Multiscale Visualization and Modeling of DNA Nanostructures

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Abstract—DNA nanostructures offer promising applications, particularly in the biomedical domain, as they can be used for targeted drug delivery, construction of nanorobots, or as a basis for molecular motors. One of the most prominent techniques for assembling these structures is DNA origami. Nowadays, desktop applications are used for the in silico design of such structures. However, as such structures are often spatially complex, their assembly and analysis are complicated. Since virtual reality (VR) was proven to be advantageous for such spatial-related tasks and there are no existing VR solutions focused on this domain, we propose Vivern, a VR application that allows domain experts to design and visually examine DNA origami nanostructures. Our approach presents different abstracted visual representations of the nanostructures, various color schemes, and an ability to place several DNA nanostructures and proteins in one environment, thus allowing for the detailed analysis of complex assemblies. We also present two novel examination tools, the Magic Scale Lens and the DNA Untwister, that allow the experts to visually embed different representations into local regions to preserve the context and support detailed investigation. To showcase the capabilities of our solution, prototypes of novel nanodevices conceptualized by our collaborating experts, such as DNA-protein hybrid structures and DNA origami superstructures, are presented. Finally, the results of two rounds of evaluations are summarized. They demonstrate the advantages of our solution, especially for scenarios where current desktop tools are very limited, while also presenting possible future research directions.

Index Terms—Virtual reality, abstraction, DNA origami, nanostructures, visualization, focus+context, interaction, in silico modeling, nanotechnology, multiscale, magic scale lens

1 Introduction

DNA nanotechnology is a rapidly growing field that concerns the fabrication of nanoscale objects, using DNA as a building material. DNA origami [53] is currently the most widely used paradigm for assembling DNA nanostructures offering promising biomedical applications. Many researchers have created nanoscale devices with a variety of functions, such as a cargo-delivering device [13], cargo-sorting nanorobots [57], and cleaving nanoscorpions [35], all based on this method. They demonstrated therapeutic applications which pave the way into the future of a novel medicine by administering nanorobots into the human body targeting a broad spectrum of pathogens [39].

Modeling DNA origami structures is a highly spatial task that has to be supported by specific visualization and interaction methods. At the same time, the constraints given by the nature of DNA has to be abided. The prevalent solutions are based on a combination of 2D and 3D representations available in desktop applications. Their main disadvantage is that the modeling operations are indirect. The user either interacts with the 2D representation, and the actions are projected onto the 3D model, or interacts with the 3D objects directly but with lacking or limited access to manipulation in all three axes. As a result, proper perception of the shape and position of the 3D objects poses a substantial cognitive load, causing reduced confidence in the design and the biological relevance of the assembled nanostructure. Since the wet lab experiments are costly and time-consuming, this confidence is an important aspect of the DNA origami pipeline. Therefore, employing technology naturally suited for spatial tasks and operations can lead to significant improvements in the design process. In this regard, virtual reality (VR) headsets and controllers with motion tracking sensors are ideal candidates, as they provide the users with additional degrees of freedom (DOF) for the intuitive analysis and interaction with spatial objects.

Hence, in this paper, we propose Vivern, a [v]isualization, [i]nteraction, and [v]irtual [e]nvi[r]o[n]ment for DNA nanostructure design in virtual reality. Our solution focuses on enhancing the spatial assembly and analysis of large DNA origami structures that often consist of several substructures. The assembled structures can be either modeled from scratch or loaded from other tools and further modified. Besides the VR modeling capabilities, we also introduce novel visualization and

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Manuscript received mmm dd, yyyy; revised mmm dd, yyyy.

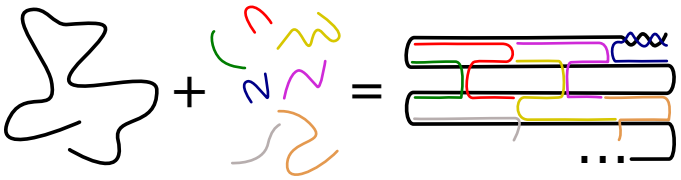

Fig. 1. The process of DNA origami assembly. The scaffold strand (black) is accompanied by several complementary staple strands (in color), together creating a final nanostructure. Two neighboring strands result in a double helix as shown in the top right corner of the image.

interaction concepts that are specifically tailored to the VR modality. By including the DNA nanotechnology experts directly into our research team (see Section 4), these concepts are designed to fulfill their needs. In summary, the contributions of our solution are:

- We characterize the domain of the DNA origami *in silico* design for VR applications. We identify the tasks and challenges and implement a system that enables scientists to model feasible DNA nanostructures in VR in an intuitive and easy-to-use way.
- We address the challenge of spatial complexity of DNA origami structures with a VR multiscale visualization concept, offering from detailed to highly abstracted representations.
- We propose two novel interaction mechanisms dealing with the density of DNA origami structures. The *Magic Scale Lens* metaphor represents a local visual embedding of different scales that preserves the locality and context of abstract representations. The *DNA Untwister* is an approach to visually straighten the helical twists of the DNA double helix to further reduce the visual complexity.
- To facilitate the interactive design process, we propose multiscale modeling operations for DNA, such as *addition*, *erasing*, *connection*, and *breaking*.

2 Background

The DNA molecule has many interesting structural properties. As the famous double-helical shape suggests, it consists of two antiparallel and complementary strands. Each of these can be described as a sequence of nucleotides, consisting of a sugar-phosphate backbone and a nucleobase. Antiparallelity means that they have an opposite direction, i.e., one goes in 5′ (five prime) to 3′ direction, while the other runs from 3′ to 5′ end. The names of the strand endings are derived from the numbering of a sugar carbon atoms. Regarding the complementarity, in the case of DNA, there are four possible types of nucleobases – adenine, thymine, cytosine, and guanine. Due to their molecular structure, only certain bases can have a bond with each other. These bonds hold the two strands together and determine the best way one strand will be matched with another. Thanks to this predictable behavior of base-pairing and the ability to exploit it, DNA is an ideal building material.

2.1 DNA Origami Basics

Due to the nanoscale nature of DNA nanostructures, special techniques are required to assemble them. Amongst available paradigms is DNA origami (see Figure 1), an approach for DNA nanostructure design presented by Paul Rothemund in 2006 [53], which relies primarily on the natural geometry and base pairing of DNA, thus allows for omitting atomistic details during the design process.

The design of DNA origami structures revolves around the folding of a single long DNA strand according to predefined rules. Commonly, single-stranded DNA of the M13 bacteriophage is used for this purpose. This strand, called *scaffold*, describes the overall shape of the structure, therefore, it is important to have a good understanding of its route and spatial placement. To ensure that the structure will remain in the desired shape, a large number of short strands, called *staples*, is used to provide complementary bases for the scaffold. Thanks to their short length, staple strands can be synthesized with a desired sequence to match the required complementary part of the scaffold. These strands pass from one double helix to the adjacent one, creating a so-called *crossover*, to make these double helices stick together. The crossovers can occur only at specific locations where the helical turns are close together. Therefore, the design of a meaningful set of staple strands and *crossover* locations also requires a good understanding of the spatial arrangement of the structure and its properties.

2.2 DNA Origami Pipeline

DNA origami pipeline starts with an *idea* that determines for what purpose the structure should be built and what it should achieve. The idea is followed by a *design*, happening, typically, in several iterations. The design is a core part of the pipeline and the main focus of this paper, as it is the step where the actual architecture of the structure is determined. Since the design offers only a static view of the final structure, it is usually followed by molecular dynamics *simulations*, trying to predict the real-world behavior of the structure. The goal of the simulations is to discover whether the structure remains stable and in the desired shape. If the simulation identifies structural problems, the design is reiterated to prevent the discovered issue. What follows in the case of successful simulations are *wet lab experiments*, where the final structure is assembled.

2.3 Lattices

To provide a good compromise between the modeling freedom and keeping biological relevance, the concept of lattices was introduced by Douglas et al. [14]. There are two basic types of lattice organization: honeycomb and square (see Figure 2). The type of lattice determines the arrangement of the neighboring double helices. This arrangement influences the locations of possible *crossovers*, which must occur at regular intervals since they are crucial for connecting double helices into a DNA origami structure. The honeycomb layout creates a hexagonal lattice in which the double helices are arranged at the vertices of the individual hexagons. Therefore, each double helix has up to three neighbors, evenly distributed with a 120-degree step. In the square layout,

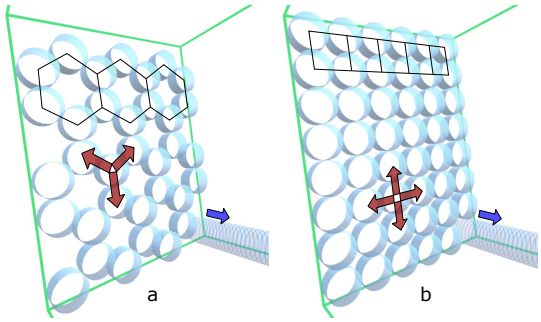

Fig. 2. Two possible arrangements of the DNA double helices: a) honeycomb lattice, and b) square lattice. The red arrows indicate adjacent double helices with which *crossovers* can happen at certain locations on the z-axis (blue arrow). The z-axis is parallel to the helical axes of the double helices.

each double helix has up to four neighbors with a 90-degree step. The choice of the lattice layout also depends on the desired shape and size of the modeled nanostructure. The use of the square lattice leads to denser structures with potentially higher structural stability. In contrast, honeycomb lattices allow the design of objects with larger volumes.

3 Related Work

This section aims to present and discuss the relevant studies and applications from the existing literature.

3.1 Molecular Modeling and Visualization on Desktop

Molecular visualization is a very broad branch of data visualization, thus we cannot aim to give an exhaustive list of the existing works in this field. For that, we kindly refer the reader to the survey by Kozlíková, Krone et al. [34].

In the following, we will focus only on the work related to modeling and visualization of DNA structures. Several 2D and 3D visualization techniques for DNA were presented over the years. An early approach for 2D DNA visualization was presented by Shapiro et al. [55]. This work is considered a standard for depicting 2D DNA structures, however, it needs manual interactions to resolve drawing overlaps caused by geometric constraints. Various approaches trying to overcome this issue were presented over time [26], [56]. Besides that, in the domain of RNA visualization, additional research focusing on semi-automatic generation of publication-ready visualizations was performed [10], [11]. As the DNA nanostructures were becoming increasingly three dimensional, appropriate visualization and modeling approaches had to be developed. The modeling itself can vary depending on the task and target structure. The users can utilize extensions of classical 3D modeling tools, such as BioBlender [54] or Molecular Maya [9]. However, in most cases, specialized tools that have been designed for interactive modeling of DNA structures [8], [29] provide better results as they can profit from narrower application areas allowing for purely DNA-focused approaches. In particular, modeling and visualization of DNA strands pose specific requirements. Lindow et al. [36] introduced algorithms for an interactive visualization of very large RNA and DNA structures. Recent work of Klein et al. [33] presented an approach for the parallel construction of DNA structures that occupy a predefined region. However, their work lacks the aspect of nanoscale modeling.

Another common issue that has to be addressed when working with DNA structures is their multiscale nature. Miao et al. [43] published a comprehensive overview of the currently existing approaches to multiscale molecular visualization. The multiscale aspect of DNA was also approached by Halladjian et al. [25], who proposed a framework for interactive visualization of genome data covering several orders of magnitude of scale. However, their approach works only with the given input data, without any options for further modeling or fitting. Similarly, Miao et al. [42] proposed a multiscale visualization concept that seamlessly crosses several semantic levels. This work was further extended into the DimSUM method [41], which proposes a novel interaction concept of a 2D navigation panel that allows seamless transitions between the individual scale levels and dimensions.

3.2 Molecular Modeling and Visualization in VR

Some of the earliest explorations of VR were focused on molecular visualization [48]. In some approaches, the user's role is primarily observational [2], [21], in others, the user can navigate in a virtual space and inspect a molecular structure from different angles [32], [50], [68], [69]. This is the case in Molecular Rift [46], an immersive and interactive 3D visualization tool for drug design, which involves a molecular viewer controlled by gesture recognition [24].

The potential of VR for immersive 3D visualization of DNA structures was also exploited in the area of genomics [65]. ADN Viewer [28] is an application for the visualization and exploration of genomic 3D structures that also integrates VR capabilities to enable stereoscopic visualization on large screens [27]. 3DGV [68] is a newer approach that focuses on manipulating data in two-controller immersive environments, but again it does not support modeling tasks.

DNA modeling is a complex task that requires specific tools and interaction techniques. The general problem of manipulation with 3D objects in virtual reality has been heavily studied in the past, covering all sorts of interaction devices ranging from traditional mouse and keyboard, through hand gestures up to VR controllers [6]. The manipulation itself is often divided into two main categories based on the number of DOF modified simultaneously – these are integrated and separated DOF manipulation [62]. Both of these approaches exhibit certain advantages and disadvantages [66], [40], depending also on the particular input device. For example, it was shown in the work of Besançon et al. [5] comparing mouse-based, touch-based and tangible interactions that in the 3D docking task, the three input modalities were comparably accurate but the tangible interaction was faster than the other two. Another study, focusing on comparison of virtual hand and 3D mouse input devices, concluded that the virtual hand was significantly faster and more accurate in their scenario involving manipulation with a 3D object. The speed and accuracy was then further improved under stereoscopic viewing conditions when compared to monoscopic results [67]. Despite the potential to provide effective 3D interactions, general-purpose tools for modeling in virtual environments, such as

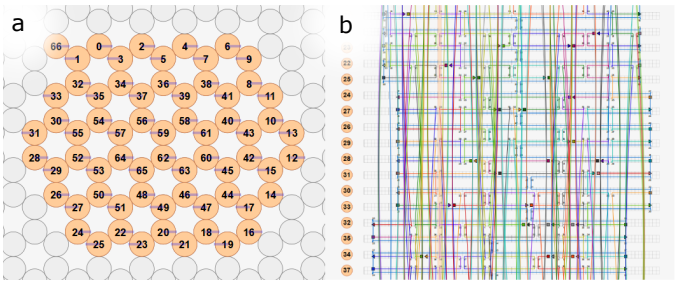

Fig. 3. a) Slice panel view in caDNAno, showing the arrangement of the lattice (xy-plane). b) In the Path panel view, the scaffold and staples (z-axis) can be drawn.

Google Blocks [23], do not provide the semantic features necessary for modeling DNA structures. To date, only a few specialized modeling tools for molecular data have been developed for VR. One of them is VR-CHEM [12], a prototype tool that allows for the construction of small molecules on the atomistic level. This approach is not appropriate for modeling DNA origami since the structures are too large to be modeled atom by atom. Another approach is CellPAINT-VR, a VR implementation of the CellPAINT tool [22], which provides illustrators with a toolbox to sketch complex cellular environments. However, modeling DNA origami structures requires specific scales and constraints, such as precise placement and linking of DNA strands. To the best of our knowledge, there is no work or tool presented in the literature that uses VR to solve this challenge.

3.3 DNA Origami Modeling and Visualization

The complexity of the DNA origami design process requires adequate support in the form of sophisticated interactive modeling tools. Several interactive desktop approaches [3], [14], [37] have been published in recent years, however, they all share the same problem regarding the lack of intuitive spatial interactions. The most relevant applications for our tasks are caDNAno [13] and Adenita [37]. CaDNAno implements the semantic constraints of the DNA origami paradigm proposed by Rothemund [53]. This tool is widely used and undeniably represents one of the enabling technologies of the DNA nanotechnology domain. In caDNAno, the user designs the DNA origami structure by defining the basic placement of the scaffold and staple strands in the projected 2D views (see Figure 3). While this is a very popular tool for creating individual DNA origami objects, its 2D schematic representations give only a few spatial cues.

The problem of limited interaction with DNA origami structures in 3D space during the design phase was recently addressed by De Llano et al. [37] in their desktop application called Adenita. It serves for interactive 3D modeling and visualization of a wide range of DNA nanostructures, utilizing ten visualization scales proposed by Miao et al. [42]. Adenita suggests various techniques for creating DNA nanostructures, similar to a computer-aided design application. However, the desktop solution still suffers from many problems with spatiality. Namely, the depth perception as well as rotation and translation operations are cumbersome, as was confirmed by our collaborating domain experts.

3.4 Focus+Context Interaction Techniques

The dense and multiscale nature of DNA origami structures leads to considerable visual clutter and occlusion. To solve these issues, the visualization community has adopted the concept of focus+context approaches, such as interactive lenses [7], [45]. The idea is to provide an alternative visual representation of a local region on demand, defining the focus area. Tominski et al. [58] published a comprehensive survey of more than 50 lens-based techniques for different visualization purposes. Viega et al. [63] first tackled the extension of 2D lenses to 3D, and several 3D lenses have been proposed since then [20], [52].

3D lens techniques are generally designed for desktop applications and face the difficulty of manipulation within the 2D interaction space. This underlines the need to adapt lenses to novel visualization environments [58]. Recently, Mota et al. [45] investigated the use of lenses for multi-geometry 3D visualizations in virtual environments. They presented a lens concept based on the combination of a spherical 3D lens and a 3D surface sticker lens. With their approach, the section of the virtual environment to be modified corresponds to a finite 3D volume of interest. In contrast, our focus+context method is not necessarily limited to a specific shape and is primarily designed for multiscale visualizations and interactions.

4 Task Analysis

The primary goal of our work is to simplify the process of DNA nanostructure design and analysis by employing adequate visualization and interaction techniques in the VR environment. The initial idea of performing this task in VR came from one of our two collaborating experts, co-authoring this paper. This expert is a senior scientist and group leader with 13 years of experience in molecular biology and DNA design. The second expert is a computer scientist with four years of experience in the development of in silico methods for the design of DNA nanostructures. Both have contributed significantly to this paper with weekly scheduled discussions, feedback, and testing over eight months. They also helped us to identify the main challenges and requirements posed on the proposed Vivern system. These are summarized in this section. Finally, additional domain experts were involved also during the evaluation of our concept, where they provided independent feedback (see Sections 10.1 and 10.2).

4.1 Design Concept

Our design study process can be perceived as a flow of several activities, as outlined by the Design Activity Framework [38]. We started with the goal of understanding the challenges and problems of the domain, benefiting from the experience of the first expert. Based on the previous work of the second expert, focusing on multiscale visualization of DNA nanostructures [41], [42], we examined suitable visual encodings. Afterwards, we started to prototype appropriate interaction designs. Both experts iteratively provided us with their feedback. Finally, when the concept seemed to meet all initial requirements, listed in the following section, we performed user evaluations to collect more detailed feedback.

4.2 User Requirements

R1: Task-specific Multiscale Visualization The dense internal structure of DNA nanostructures is posing specific challenges on the design of appropriate visual representations. It is necessary to help the user perceive and understand the structure's internal hierarchy by providing appropriate abstraction. The internal organization, such as the position of scaffold and staple strands, should be visually communicated on demand. This can help to reveal potential problems with the biological relevance of the assembled DNA origami. On the other hand, it is equally important to provide the user with an overview of the overall shape of the structure, while omitting internal details.

R2: Interaction Modalities for DNA Origami in VR DNA origami structures are inherently spatial, so an essential part of the design process requires appropriate 3D interactions. Objects in the scene must be aligned in space, which requires simultaneous rotation and translation operations.

As the analysis and modeling operations are usually only associated with specific locations in the structure, they do not require to change the entire visual representation. Therefore, the experts' natural requirement is to be able to change the representation locally to perform the analysis and modeling tasks efficiently. This is a typical problem that focus+context techniques can solve.

R3: Multiscale Modeling of DNA Origami in VR When modeling, the expert would potentially be able to create arbitrary DNA strands in 3D space. However, without semantic constraints, it is impossible to assure that these structures are following the rules for successful wet lab assembly. Therefore, we have to integrate the semantics of the DNA origami paradigm into the interaction space. The key challenge here is to find the right balance between enforcing constraints and allowing freedom in the design.

Besides that, not only the visual inspection of the structure requires several semantic levels, but, more importantly, the interactive modeling tasks as well. The user expects that individual operations, such as removing a part of DNA, behave consistently when applied to different semantic levels. Therefore, the level of abstraction must be adapted to the task the user wants to perform.

5 Overview of Vivern

The requirements mentioned above are reflected in the design of Vivern's virtual environment, which is shown in Figure 4. The core of Vivern is formed by a virtual laboratory set up on a room-scale, in which the user can work with a six DOF head-mounted display and two remote controllers. The application is implemented in the Unity engine [60] and is designed primarily for the HTC Vive [30] and Oculus Rift [47] headsets. OpenVR [61] and Oculus SDKs [17] provide access to these devices, while Unity's XR Interaction Toolkit delivers the core VR interactions.

Each of the two controllers can apply our visualization and modeling concepts throughout the operations described in this work, while the user can move freely around and inspect the structures from various distances and angles. The virtual environment itself consists of a simple ground and a skybox.

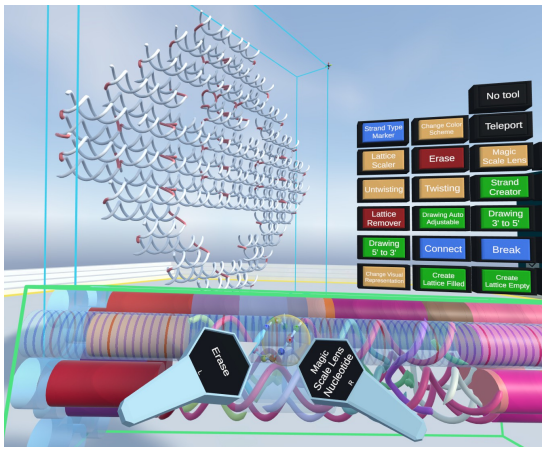

Fig. 4. Screenshot of the Vivern application capturing the user in action. The structure visualized using the single strand scale can be seen in the background while in the foreground, the user locally changes the scale of the part of the DNA strand to remove a single nucleotide. The menu placed on the right lists all available tools.

Vivern enables to create entirely new structures from scratch by defining a lattice, delineating a valid constrained modeling space as described in Section 8, that has a bounding geometry of a cuboid. To enhance the versatility of the tool and facilitate the modeling process, it also incorporates the option to load existing models, pre-designed in desktop applications. Thanks to this, we do not force the user to remodel the structures if it is not necessary. Instead, the user can fully focus on the spatial assembly or analysis while still having the possibility of further modifications.

When the modeling space for individual structures is defined, the user can design the structures using a set of modeling tools. This process is supported by different visualizations – ranging from several semantic scales of the structure, through different color schemes, up to novel focus+context techniques. To fit the experts' established workflow, Vivern supports the export of the sequences of the final designed model in a FASTA [49] format.

Despite being aimed at DNA origami nanostructures, Vivern also supports loading of proteins in the PDB format [4]. Such structures cannot be modified, but they can be freely translated and rotated, while their scale is ensured to stay consistent with the rest of the structures in the scene. This allows for creation of protein-DNA hybrid structures.

6 Multiscale Visualization

Before we dive into the VR modeling capabilities of Vivern, we need to describe the proposed visualization concepts as they are of crucial importance for almost every task. These concepts are specifically tailored to DNA origami structures as they carry features at several levels of detail, each of them suitable for particular analysis and modeling tasks.

6.1 Semantic Scales

The multiscale approach was already examined by Miao et al. [42], who proposed ten different semantic scales for DNA structures, ranging from the highly abstract tubular representations of the double strand to its atomistic details.

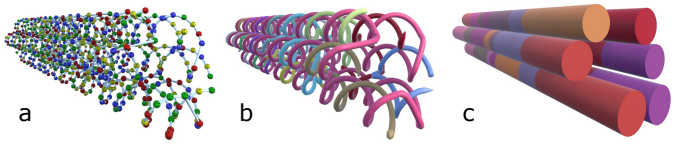

Fig. 5. Three semantic scales supported by Vivern. The level of abstraction increases from the nucleotide scale (a), through the single strand scale (b), to the double strand scale (c).

Since Vivern is focused on more coarse-grained tasks, such as the composition of DNA origami superstructures, only a subset of these scales is relevant for challenges tackled by our VR solution. For this reason, the most detailed atomistic representation can be omitted – such rather rare fine-grained operations can be better performed in a specialized desktop application. Furthermore, the information provided by some of the ten scales can be equally expressed via combination of color schemes and focus+context techniques provided by Vivern. Therefore, Vivern utilizes only a set of three expressive scales proposed by Miao et al., which visually encode the levels of nucleotides, single strands, and double helices, as shown in Figure 5. Each of these proposed scales emphasizes features of the structure that the other scales are not clearly communicating. The user is free to change the scale at any time to work with the most suitable visualization for the current task.

Nucleotide Scale: This is the most detailed scale our approach offers (Figure 5a). It represents each nucleotide by a bead with a label. The bead's color depends on the current color scheme, while the label is a one-letter abbreviation of the base type (A, T, C, or G). Since some visual tasks relate to the sequences, as they determine the binding behavior of the strands, this scale aims to provide this level of detail. The beads are joined together with cylindrical bonds to represent the topology of the strand. The bond has a decreased radius in the 3′ direction to create a sort of arrow-like shape visualizing the direction of the whole strand. The main advantage of the nucleotide representation is the ability to distinguish between individual nucleotides allowing to better perceive the size of the structure with regards to the number of base-pairs. It also allows the user to estimate the ratio of bases in the structure, for example, the important guanine-cytosine content. From the interaction perspective, this scale is most suited for nucleotide-by-nucleotide operations.

Single Strand Scale: This is the first higher-level abstraction derived from the nucleotide scale. Here each strand is visualized as a single colored tubular object (Figure 5b). The directionality of the strand is visualized as an arrow-shaped ending at the location of the 3′ nucleotide. The tube's radius equals the radius of nucleotide beads in the previous scale to preserve consistent spatiality when changing visual representations. Since the single strand scale focuses on the distinguishability between individual strands, it is suitable for visualizing the strand behavior. The individual strands, their helical twists, and existing *crossovers* are easily observable on this scale. It is also helpful for spotting high-level design mistakes, such as too short or too long staple strands.

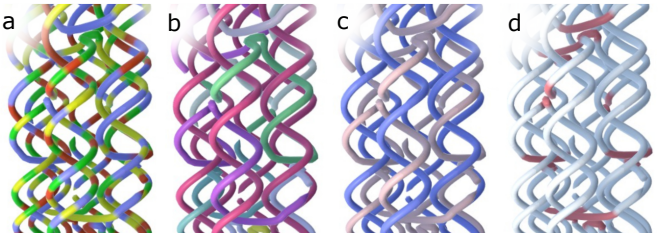

Fig. 6. Four color schemes supported in Vivern and demonstrated on the single strand scale. While a) and b) highlight general DNA parts – nucleotides, respectively individual strands – c) and d) emphasize DNA origami-specific features, namely the scaffold strand and *crossover* locations, respectively.

Double Strand Scale: When viewing large DNA nanostructures, the nucleotide and single strand scales can become visually too cluttered. Therefore, this representation merges two intertwined single strands, which define the DNA double strand, into one object represented by a cylinder (Figure 5c). The diameter of the tube is derived from the diameter of the DNA double helix. Generally, this scale is used to represent the overall geometry of the DNA origami model. At this level, the user can work with the general shape of the model without paying attention to the details.

6.2 Color Schemes

While the semantic scales help to deliver different views on the structure to highlight its various properties, additional information can be visualized, and possibly emphasized, also through color. For this reason, Vivern supports several color schemes, as shown in Figure 6, which can be applied to any semantic scale.

Nucleotide Color Scheme: This color scheme visualizes individual nucleotides with a distinct color (Figure 6a). Therefore, it is useful for the identification of particular sequences, for example, long repeating ones. To comply with the existing standards in the coloring, the colors were chosen based on the DRuMS color scheme [15].

Strand Color Scheme: This color scheme visualizes individual strands with a distinct color to support their visual separation (Figure 6b). This helps to better understand the length and path of individual strands.

Scaffold Color Scheme: Since the scaffold strand is a core part of every DNA origami nanostructure, Vivern also includes a color scheme using separate colors for the scaffold and all the staple strands (Figure 6c). For the scaffold, blue color was chosen since it is quite distinct, especially compared to the intentionally rather bland color of the staples. Also, caDNAno software uses blue color for the scaffold, so the experts are already familiar with its meaning. Thanks to this scheme, it is easier to see how the scaffold is exactly routed.

Crossover Color Scheme: This color scheme emphasizes *crossovers* as they are of crucial importance for the DNA origami nanostructure. The *crossovers* are visually distinguished from the rest of the structure by using red color (Figure 6d). It mainly helps to understand where the *crossovers* are happening, if this happens at regular intervals, and whether any anomalies occur.

7 VIVERN INTERACTIONS

In Vivern, we utilize space-multiplexing [18] in a form of two standard controllers with integrated six DOF. These controllers allow the user to directly interact with the environment as they naturally serve as the user's virtual hands. Thanks to the precise spatial tracking, the rotation and translation operations become as simple as grabbing an object and placing it arbitrarily in the space (R2). Furthermore, the mutual independence of the controllers allows the user to perform an operation with one hand, while the other hand can be used to simultaneously perform a different one. To simplify the control scheme, Vivern also introduces a tool system that allows users to equip any controller with the desired tool, selected from a menu (see Figure 4). The operations performed by the controller then behave according to the equipped tool.

Focus+Context Techniques

Without additional adjustments, the default interactions in the VR environment are not sufficient to solve all the challenges connected to the exploration and modeling of DNA origami structures. Any visualization scale can suffer from potential problems due to the size of the structure and the distance to the viewer. Namely, for large structures, the nucleotide scale can easily become cluttered, especially when viewed from a distance. On the other hand, the higher scales show too little information when viewed from close up. Another problem arises from the density of the model. In this case, the structure may be self-occluding, i.e., some parts of the structure may hide its other parts. While the multiscale visualization approach can solve the occlusion problem by reducing visual details globally, it is still challenging to inspect parts of the structure at different scales simultaneously (R2).

In this context, we present two interaction concepts, the *Magic Scale Lens* and the *DNA Untwister*. These spatial focus+context approaches change the local representation using a lens, which is a spherical volume attached to the virtual controller. The idea of lenses itself is well-known concept in the visualization domain and they can have various properties [59]. In our case, the lenses are more than just a visualization tool as they may also modify the means of interaction in the respective parts of the structure.

Besides that, both the Magic Scale Lens and DNA Untwister work in two modes. First, they provide a temporary view of the changed geometry within the focus region while hovering. Even during this preview, interactions in the focus area behave consistently according to the given scale, allowing the user to perform desired actions with the second controller. Finally, after pressing the trigger button, the new geometry is retained even if the controller moves away. This way, several different locations can be simultaneously locally changed to a more suitable representation.

Magic Scale Lens

The Magic Scale Lens (Figure 7) allows to arbitrarily change the semantic scale of any region of the structure. The main idea of this approach is that the focus region should convey information on a particular level of detail, while a more abstract representation can represent the context. This way, unnecessary visual clutter can be reduced, and the user can more easily focus on desired areas. A lower scale can be embedded in any higher one, so the details in the focus region are displayed on demand. In contrast, a higher scale can also be embedded into a lower scale representation, which shows fewer details if desired. Additional advantage of embedding of scales is a possibility to produce many different permutations of scale representations. In the work of Miao et al. [42], their multiscale approach changed the representation globally, i.e., the whole structure was always represented in a particular scale. Vivern, however, allows to arbitrarily combine the scales for more precise adjustment of the level of abstraction.

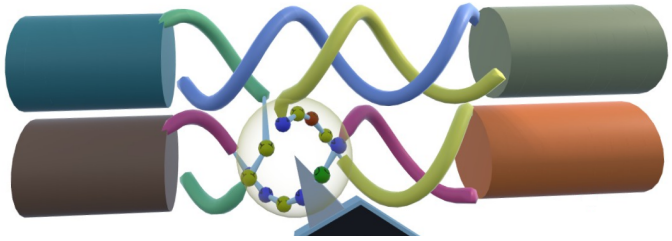

Fig. 7. The Magic Scale Lens concept. The single strand scale (focus) is permanently embedded into the double strand scale (context). In the spherical lens, we get a temporary glimpse into the nucleotide scale (focus) from the single strand scale (context).

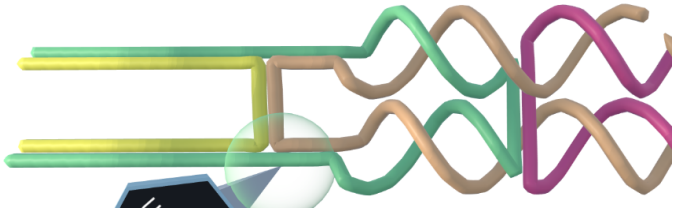

Fig. 8. Application of the *DNA Untwister* onto the double helix to reduce the visual complexity and occlusion.

DNA Untwister

The helical twist of the DNA and the spatial conformation of the nucleotides are important for understanding the structural behavior and composition of DNA origami structures. However, this information also leads to visual complexity, which can be distracting or can cause occlusion problems. Since it is not always necessary to see such details, an untwisted DNA representation on demand greatly simplifies the overall visualization without losing the two-strand depiction. Therefore, we propose the concept of *DNA Untwister*. Inside the lens, the helix is untwisted into two straight parallel strands (see Figure 8). They run parallel to the helical axis of the DNA. Of course, the untwisted depiction is very abstract, and the spatial conformation is far from being biologically relevant. However, these abstract depictions of DNA are not uncommon and can further ease the design process. For example, when combined with single stranded semantic scale, the paths of individual strands are better readable when the helices are untwisted. Once the user is finished with the untwisted conformation, the reverse operation, *twisting*, restores the original double helical shape.

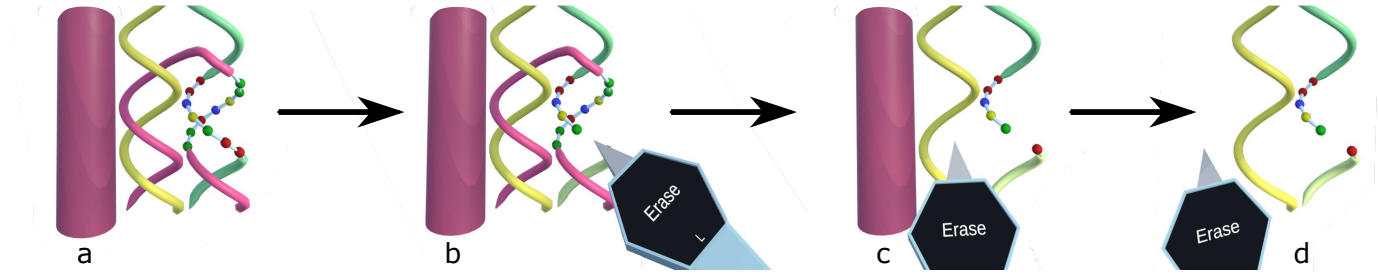

Fig. 9. Effect of the Erase operation when applied to three different scales. (a) Representation with all three semantic scales, (b) state after erasing a single nucleotide, (c) then after erasing a single strand, (d) and finally after erasing a double strand. Note that in (c), we removed the single strand which was crossing over from one double helix to the neighboring one.

8 Multiscale VR Modeling

The modeling paradigm reflects the multiscale nature of DNA nanostructures (described in Section 6.1) to provide an easy-to-use toolset. Individual DNA origami models are placed in their own lattices delineating the space where the DNA origami paradigm is valid, thus representing the area for constrained modeling (R3). The lattices can be freely positioned to allow the users to design more complex higher-order assemblies. Within the lattice, the user can create nucleotides, single strands, or double strands and then modify them using multiscale operations.

8.1 Lattice-Scale Operations

When modeling, the user is limited to model within the lattice that imposes strict rules for positioning DNA double strands, hence, reducing the effort in the spatial arrangement of DNA strands and also helping with the creation of the biologically feasible final structure. On the other hand, this model gives the users full control over the position of individual lattices in the scene, allowing them to freely assemble higher-order superstructures.

The user can either start modeling from scratch or load an existing model and take it as the basis for further modifications. In the latter case, the lattice parameters can be automatically retrieved from the loaded model. However, during modeling from scratch, the user needs to define these parameters. This is done by selecting the desired lattice type, followed by drawing a cuboid describing lattice dimensions and orientation. As previously described, the potential *crossover* locations force the double strands into certain patterns, formed by the honeycomb or square arrangements we extended to 3D (see Figure 2). To simplify the design process, the user can decide whether the lattice should be created empty or pre-filled with double helices. We call this additive, respectively subtractive, modeling. The former is the standard approach and suitable for those tasks, where the custom shape is rather irregular. For models densely occupied by the strands, it can be more beneficial to utilize the subtractive mode, resembling the sculpting process, when the user is removing DNA strands to reach the desired shape.

When the controller moves inside the lattice, a semi-transparent cylinder appears at that position. It shows the potential length and radius of the double helix and additional circles that indicate the base-pair positions and the potential crossovers. The neighbouring double strand locations are represented by semi-transparent cylinders, while the back side of the lattice visualizes the whole lattice layout. This allows the user to identify valid locations for strand positioning and simplify the neighboring double helices' alignment. Since the visualization of the lattice might occlude the objects inside, the user can temporarily hide it even when the controller is inside the lattice. The same applies to the cuboid wireframe.

8.2 Structure-Scale Operations

While lattice-scale operations served to determine the modeling space and constraints for the structure inside the given lattice, the operations described in this section modify the structure itself in various ways. They can be divided into four main categories.

Create operations, realized via various tools (Section 7), add a new part of the structure. On the lowest level, it is possible to draw strands of an arbitrary length and direction in a nucleotide-by-nucleotide manner by pressing the appropriate controller button and moving the hand in the desired direction. If a nucleotide from one single strand is neighboring a nucleotide from another single strand, these two single strands are automatically connected via these nucleotides to form one continuous single strand. If two nucleotides occupy the same lattice cell, they are identified as a base pair. The previous operation is extended by the so-called auto-adjustable drawing. This tool creates a single nucleotide or a base-pair in the appropriate direction. The decision is automatically made by Vivern, based on the neighboring element. Moreover, the new element also shares the neighbor's visual representation, as described in Section 6.1, to create a consistent continuation of the existing parts of the structure. Users can also create complete double or single strands at a given position, filling the whole row of the lattice. The newly created strands are then filled with an arbitrary sequence of nucleotides. In the case of a single strand, users can also choose its direction – from 3′ to 5′ or from 5′ to 3′. This operation matches the type of the created element with an appropriate visual scale. Therefore, single strands are spawned in a single strand representation, while double strands are automatically visualized with double strand cylinders.

Erase operation enables removing a geometry at all scales. Users can remove individual double helices, single strands, or individual nucleotides by switching to the erase

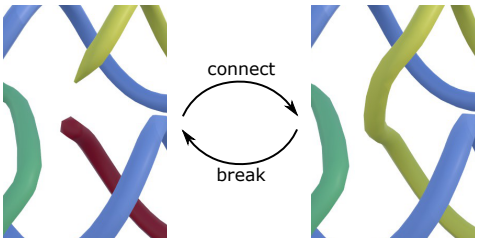

Fig. 10. Complementary operations of connecting and breaking on the single strand scale. When connecting, two strands belonging to the neighboring double helices (red and yellow in the left image) will be merged into one strand, resulting in a *crossover* (yellow in the right image).

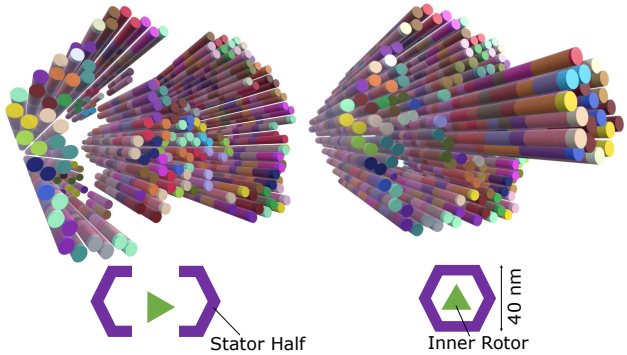

Fig. 11. Assembling the superstructure from three individual DNA origami components: two stator half components and an inner rotor. The result is an assembled rotary device.

mode and clicking on the objects in the 3D space. Thanks to the multiscale nature of this operation, its effect depends on the scale it was applied to (see Figure 9).

Connect operation, available only at the single strand and nucleotide scales, enables the user to create a bond between two nucleotides to join two single strands into a continuous one. Thus, it allows to create crossovers (see Figure 10), a crucial part of every DNA origami nanostructure.

Break operation allows the users to break the bond between two nucleotides (see Figure 10). This operation is available only at the nucleotide and single strand scale levels and serves two purposes. First, by breaking a bond, the strand is split into two new strands, and then, by applying the Erase operation (on the single strand scale), these two parts can be removed independently. Second, disconnecting nucleotides allows the users to create ends that can then be joined with other strands using the Connect operation, e.g., to make a crossover.

9 Case Studies

The need for new design tools arises from the research in advanced and novel nanodevices that are difficult to design using traditional tools. To demonstrate the capabilities of our approach, the nanotechnology expert in our team designed the following three case studies involving an assembly of various structures. With the commonly used caDNAno [13] tool, the assembly of such complex structures is impossible, as it can handle only a single component at a time. In Adenita [37], having better support for 3D viewing and modeling than caDNAno, it is possible to assemble some of the structures presented here. However, the positioning of objects in space is far from being intuitive and fast enough using its 2D interface. Furthermore, the impaired spatial perception can make it difficult to align the structures or to understand how they are exactly located with relation to each other. In general, none of the existing desktop solutions offers the combination of the constrained modeling and free-form positioning of lattices in space.

As the case study was performed in the COVID-19 outbreak, it had to be completed remotely. The expert navigated the actions of another team member, who had access to the VR headset, by commenting on the individual steps. Observations of the expert are summarized along with the descriptions of the cases in the following text.

Case Study 1: DNA Origami Superstructures The first and one of the most important features that Vivern supports is the multi-component design of several DNA origami structures, assembled into a superstructure. We demonstrate this functionality using a rotary device design proposed by Ahmadi et al. [1]. As can be seen in Figure 11, we load two components of a stator and one inner-rotor component and connect them into a rotary device. According to the expert, it is crucial to see how several components can be put together. Using our approach, they can be easily spatially fitted. As these are rather large structures, we switched the visualization to the double strand scale to gain a better overview. The inner-rotor is then placed inside the stator. We can easily inspect whether the rotor has enough space to rotate simply by testing its rotation motion using the controller. Based on this, the domain expert suggested that it might be interesting to add the possibility to animate the components to better understand the dynamic behavior of the rotary device.

Case Study 2: Hybrid Structures Another very important use case, according to our expert, is the generation of hybrid structures that contain both proteins and DNA. In Figure 12, we demonstrate the design of an artificial protein-DNA complex that uses the DNA structure as a container to hold the protein active site in the center [31]. According to the expert, such a structure can emulate the catalytic activity of an enzyme by replacing a large part of the protein complex with the DNA-based structure. First, we load and connect the two half shells, followed by moving the loaded protein to the desired location. Afterwards, we create the empty square lattice and then fill it using the additive approach to get carrier strands of an appropriate length. Then we position the carrier strands such that they are connected to the shell structure. Two parallel double stranded carrier strands are then modified using our *break* and *connect* operations. At the proximity to the protein, we locally switch the scale of DNA to the nucleotide scale using our Magic Scale Lens. In this scale, the proximity of the individual nucleotides to the amino acids is easily visible. This can be later used for adding cross-linkers on the nucleotide level. The expert commented that the different scale levels adjusted using the Magic Scale Lens are tremendously useful, as often only a small part of the structure has to be inspected in detail.

Case Study 3: Designing Custom DNA Origami Components Our system allows experts to create custom shapes

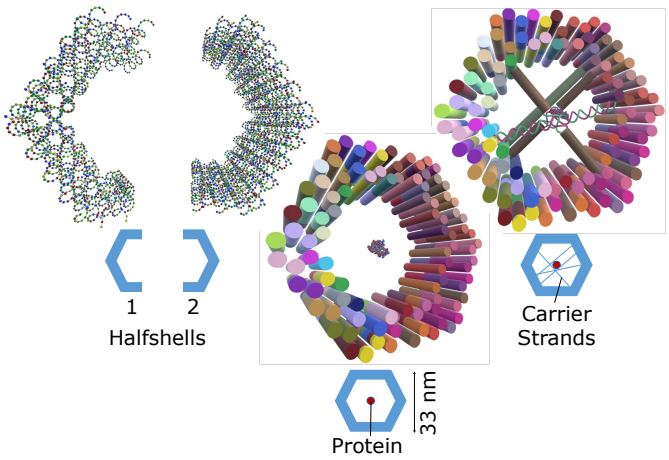

Fig. 12. Hybrid structure built from two half shells of DNA origamis that are first super-assembled together. Second, a protein structure is positioned into the center of the assembly and then bound to the assembly by the carrier DNA strands.

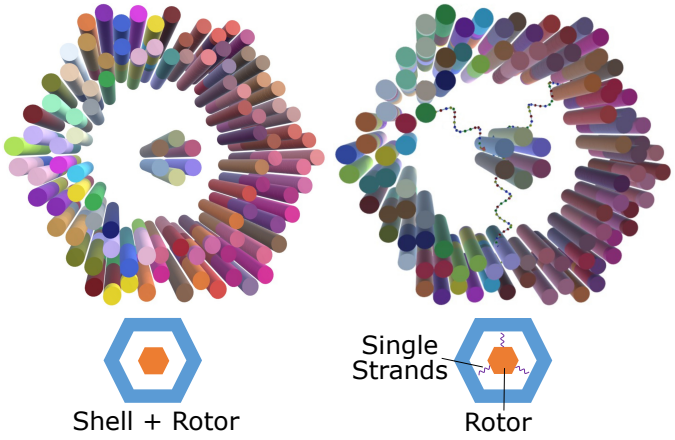

Fig. 13. Assembling a rotary structure by positioning a rotor inside a shell (stator) and connecting these with three non-parallel single strands.

in VR as well. Figure 13 presents the prototyping of a rotor that uses strand displacement to create rotary motion. We use the same shell structure as in Case Study 2; however, we add a hexagonal rotor in the center. We use the lattice-constrained design to create an empty honeycomb lattice and add six double strands using our multiscale modeling approach. This newly generated component is then placed into the center of the shell structure. Furthermore, three off-axis single strands are added in order to facilitate a DNA walker approach [51].

Summary The case studies demonstrated the possibilities of our concept and also revealed some of its limitations. It was shown that the Vivern can be used for an assembly of novel nanostructures and that the proposed interaction and visualization concepts support this task. As for the limitations, except for the desire to animate individual components, the expert also suggested the possibility to select more components with a single controller at the same time, in order to perform their simultaneous transformations. Finally, he also noted that implementing an algorithm for automated scaffold routing would be very helpful for real-world applications. This is something which we will examine in the future.

10 User Study

We conducted a user study which was designed as a two-stage evaluation with seven experts from the field of DNA nanotechnology and relevant domains to gather their valuable feedback.

Three experts, involved in the first stage, participated in a remote testing procedure described in Section 10.1. These sessions were held remotely due to the experts being located in research institutions worldwide. The goal here was to gather feedback from completely independent experts and see their opinions about our concept. The first participant is a postdoctoral researcher and experimentalist with a focus on biosensing using DNA-based structures. The second one, also a postdoctoral researcher, is a physicist focusing on creating in silico DNA models for simulation. The third one, a second-year PhD student in physics, focuses on coarse-grained simulation of DNA structures. They all have experience with the currently available DNA modeling tools.

Additional four experts participated in an on-site testing procedure, detailed in Section 10.2, aimed at hands-on evaluation of the Vivern usability. The first one is a senior scientist specialized in DNA-based diagnostics. The second expert is a fifth-year PhD student in Biotechnology and an expert in the self-assembly of DNA origami structures. She has done research in the assembly of novel superstructures. The third participant is a fourth-year PhD student whose focus is on computer-aided design and simulation of custom DNA-protein hybrid structures. The last expert is a postdoctoral researcher in molecular biology, working on the functionalization of DNA origami structures.

10.1 First Stage – Evaluation of the Initial Concept

We prerecorded a video demonstrating the individual features of our system and shared this video with participants. Then, within the semi-structured remote one-to-one interviews, we used a questionnaire, provided in a Supplementary Material, consisting of 13 questions to gather feedback about the whole concept and let the experts share their opinions. Here, we tried to stress out that we are not evaluating an entire fully-fledged system, but the necessary visualization and modeling concepts in VR.

10.2 Second Stage – On-Site Evaluation

The second stage of user testing followed the Think Aloud protocol [19] and was held on-site, which was possible thanks to the less strict COVID-19 rules at the time of testing. The participants had little or no previous experience with VR and were tested individually. This evaluation was performed on a system version presented in this paper. We prepared a testing procedure, limited to maximally one hour, consisting of four basic steps – (1) introduction to the testing procedure and VR hardware, followed by (2) introduction to the Vivern application, its environment, and basic concepts, then by (3) performance of modeling, analysis, and assembly tasks, and finally by (4) post-testing discussion. In the first step, the focus was on explaining

the purpose and length of the testing, our expectations, and VR equipment and its usage. As the second step, each participant was introduced to the Vivern application, and with a VR headset on, they tried all its important features. We already started to gather initial feedback, trying to understand what the first impressions are and how difficult it is to get acquainted with the application for users without any prior VR experience. The third step was the most important one. We were trying to verify our assumptions about the types of tasks for which Vivern is supposed to be the most suitable tool. For this purpose, we split the performed tasks into three main categories: *modeling from scratch*, *analysis and visualization of the existing structures*, and *assembling the superstructures*. Later on, these categories also served as a high-level basis for the deductive Think Aloud coding scheme used for the analysis of the study transcripts. The transcripts themselves were created by one of the team members who was present during the individual testing sessions and noted down all comments and observations. Furthermore, based on these categories, several test structures were prepared, designed with a particular task in mind. If the experts provided us with suitable caDNAno structures of their choice, they could use these during the individual tasks instead of those prepared by us. This way, not just the capabilities of Vivern were verified, but the experts could also directly experience the difference between our concept and the existing solutions they use. Finally, when the experts finished the tasks, we proceeded with the discussion about the benefits and disadvantages of our VR solution for their work.

10.3 User Study Results

This section summarizes the outcomes of both conducted user studies. It is based on the written transcripts containing comments of the participants and our observations.

During the first stage, all involved experts raised the need for improved spatial understanding in their current work and were positively surprised that there is a tool like Vivern that aims to handle this issue. One expert mentioned that better spatial understanding would be beneficial for DNA origami and protein hybrid structures. Another participant pointed out that Vivern might be great for the assembly of larger structures from individual building blocks. In this case, a cylindrical double strand semantic scale was considered as especially beneficial for getting the overview. Furthermore, all of the experts considered the creation of initial conformations for coarse-grained simulations as a very promising application scenario for such a tool since this task involves mainly spatial interactions. Finally, our proposed focus+technique concepts were considered as very novel and practical. One expert noted that the *DNA Untwister* could be particularly useful for scaffold strand routing.

Regarding the second testing stage, the consensus among the participants was that the VR environment provides a far better spatial understanding than any of the existing approaches they use. One expert said: *"the biggest advantage of VR is an intuitive change of perspective."* Another one stated that *"Despite 2D [tools] are better for some tasks, I would prefer VR over 2D for assembly of multiple structures."* In this case, he was specifically referring to the simplicity of spatially aligning one structure with another. Regarding the 2D preference, he concluded that he would find the 2D interface more approachable for analysis of a DNA sequence. This expert also added that *"caDNAno is simple, but it has severe restrictions as the only alternative to free form modeling is specifying a sequence which only advanced users can do."* Another participant appreciated the ability to enter his own molecule to Vivern as it gave him an alternative perspective onto their structure of interest. He enlarged the structures, so they started to resemble buildings. In this situation, he would appreciate the ability to fly up, which is currently not possible, but we will consider this for a future version. Another highly appreciated functionality was the ability to locally change the scales using the Magic Scale Lens. Several participants used this functionality when working with the break and connect tools to reduce the visual clutter. One participant suggested adding the ability to make the context (outside the Magic Scale Lens) completely invisible. Another participant indicated that the Magic Scale Lens could be very useful for generating figures for publications. For instance, when an existing origami structure is modified, the updated parts could be presented in more detail to emphasize the changes.

As two experts did not prepare their own structures of interest for the analysis tasks, they were presented with a structure that was unfamiliar to them and we modified it in a way that some of the strands were intentionally incorrect. The participants were not aware of this problem, as the goal was to test if they can discover that the structure is incorrect on their own, while freely inspecting the structure. The first participant spotted this error almost immediately after loading the structure from the 3D representation itself. He then decided to fix the problem, which was very easy using the connect tool. The second participant spotted the problem within a minute, after selecting coloring based on the individual strands. Relevant to this is a comment of one of the participants that Vivern can be very useful for discovering structural errors, possibly caused by the design mistake made by another researcher. He stated that it can be easier and faster to understand the structure from the available 3D representations than by having a look at a caDNAno design, for example.

Generally, the various coloring schemes proved crucial for some of the tasks. For instance, it allowed participants to quickly identify scaffold strands or get an overview of how many crossovers are present.

However, the experts also identified some drawbacks and possible future improvements. For instance, one participant suggested adding the ability to snap the individual latices to a grid when positioning them in the 3D space. He also noted that the exact alignment of parts can be difficult, as the controller has to be held still in 3D space. For this, he suggested to add support for standard gizmos. The issues with precise alignment are side effects of the integrated DOF manipulation, which is generally usable but not perfect for precise operations. In this case, employing separated DOF techniques complementing the integrated ones, for example in a form of aforementioned gizmos modifying only selected translation or rotation axes, would be desired. Another participant would like to see the support for calculation and depicting molecular dynamics within the

VR environment. Some participants suggested visualizing the direction of strands despite this being already depicted (as described in Section 6.1). This means that such encoding is insufficient, and we are planning to experiment with alternative encodings in the future. Finally, two participants were experiencing troubles when placing the menu in the 3D space, as it sometimes interfered with other interactions. One participant also suggested using icons instead of a text in the menu.

Based on the results of the conducted user study, Vivern turned out to be well tailored to tasks involving the assembly of several structures, as well as to the analysis of individual structures. This confirms that better spatial understanding and interaction provided by the VR medium, combined with appropriate visualization techniques, can be beneficial in this scenario. Regarding the modeling from scratch, Vivern can be used for this purpose, but the disadvantages of VR, such as overhead with setting up the VR equipment and increased fatigue, can overcome its advantages in this particular case.

11 Conclusion

As the field of DNA nanotechnology is growing, researchers are aiming to develop more complex and capable nanostructures. To facilitate their work, we proposed a visualization, interaction, and virtual environment for DNA nanostructure design in virtual reality – Vivern. Our concept combines the state-of-the-art VR technology with appropriate visualization and interaction concepts. We propose lattice-constrained modeling approach offering freedom in the design, while meeting necessary modeling constraints. Then we suggest advanced modeling multiscale operations to facilitate the design process. To overcome the challenges posed by visualization of DNA nanostructures, we propose specialized focus+context techniques, multiscale visualizations and color schemes. While we focused on DNA origami structures, we believe that the proposed concept of multiscale visualization and modeling can also be applied to other data with similar properties. On a conceptual level, our multiscale local visualization can suppress or eliminate visual clutter in brain fiber tracks [16] or in Connectomics data [44] due to their similar properties. Multiscale modeling is a concept that can potentially be applied to all types of multi-level phenomena, where data must be modified interactively in 3D space.

Furthermore, we demonstrate the usefulness of the proposed approach by modeling novel nanodevices based on the recent research advances and requirements in this area. Finally, we conducted a user study with experts which helped us identify strong points of the current solution, which should be more deeply examined in the future. It also pointed out places for improvement, as well as new interesting research directions. Based on the received feedback, we believe that such a VR concept can be successfully applied to fulfill specific needs during the DNA origami design pipeline. Thanks to that, precious time and money can be saved by reducing the number of design mistakes and deepening the understanding of the structure's spatial layout. As two of the participants mentioned, the Vivern concept can also be very useful for education and learning purposes, as it might provide the users with better insight into the fascinating world of DNA origami structures. Regarding the limitations of our concept discovered during the user study, we believe that most of them can be solved by employing additional VR interaction or visualization techniques.

For future work, we plan to move towards our ultimate goal of providing a useful novel system for researchers in the field of DNA nanotechnology. From the discussions with experts, we have already collected a list of interesting novel features. Namely, understanding the dynamic behavior of the designed structures under certain in vitro conditions is necessary before conducting the wet lab experiments. Therefore, a visual analysis approach for coarse-grained simulations, such as oxDNA [64], would be a very interesting future research direction. Furthermore, we see our system as a potentially effective tool for the assembly of nanostructures. This idea would greatly benefit from a more developed DNA data model combined with a template library, from which many pre-created nanostructures would be selected and assembled together.

Acknowledgments

The presented work has been supported by the Ministry of Education, Youth and Sports of the Czech Republic under the INTER-COST research project no. LTC20033. This research was also supported by ILLVISATION grant by WWTF (VRG11-010) and by the King Abdullah University of Science and Technology (KAUST) Office of Sponsored Research (OSR) under Award No. OSR-2019-CPF-4108. This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No. 952110 (MARILIA). We also would like to thank Vojtěch Juřík for his help with the formal parts of the case study and user study. We would also like to thank all experts involved during the user study for their time and valuable feedback.

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